COVID-19, cardiovascular disease and multimorbidity: a learning health system approach

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Over two years into the COVID-19 pandemic, cardiovascular disease (CVD) has emerged as a risk factor for severe acute direct[1], indirect[2] and longer-term effects, and an outcome of both acute COVID-19 and Long COVID[3], which can affect up to 54% of COVID-19 survivors[4]. Risk of CVD post-COVID-19 has been studied in specific settings or cohorts (e.g. hospitalised individuals), for overall CVD or certain categories of CVD (e.g., acute coronary syndrome). However, the full spectrum of CVD is not well characterised in Long COVID over the long-term. Long COVID presents a major burden across countries. For example, 1.1 million people in the UK have persistent post-COVID symptoms beyond 12 weeks[5]. Advances in science, evidence and care are urgently needed in a "learning health system" approach to effectively mitigate against impact on Long COVID, including CVD complications (Figure 1).

Science

Xie and colleagues systematically examined the risk of incidence of a wide range of CVD subtypes one year post-COVID-19 in 153,760 individuals from the US Department of Veterans Affairs (VA) national database, comparing with control groups before and during the pandemic[6]. They report increased risk and excess burden for incident cerebrovascular disorders such as stroke (hazard ratio, HR 1.52, 1.43-1.62), dysrhythmias such as atrial fibrillation (HR 1.71, 1.64-1.79), ischemic heart disease (HR 1.72, 1.56-1.90), inflammatory heart disease (pericarditis: HR 1.85, 1.61-2.13, and myocarditis: HR 5.38, 3.80-7.59), heart failure (HR 1.72, 1.65-1.80) and thromboembolic disease (HR 2.93, 2.73-3.15) among those with SARS CoV-2 infection (non-hospitalised, hospitalised and admitted to ICU) who survived the first 30 days.

Potential mechanisms include chronic inflammatory response induced by viral persistence in heart tissue, molecular mimicry invoking an autoimmune response to cardiac antigens and persistent endothelial and microvascular disfunction[7]. For example, a recent study of 70 consecutive patients (62.9% male; mean age 54.5 years, 32.9% acute COVID-19 hospitalisation) in a dedicated post-COVID-19 outpatient clinic in Greece, suggested that

arterial stiffening, endothelial dysfunction and a persistently high oxidative burden may contribute to cardiac dysfunction, which had not fully recovered at 12 months, compared to controls[8]. Further prospective research must address underlying biological mechanisms and predisposing risk factors to guide investigation and treatment strategies.

Evidence

Multiple shared cardiometabolic risk factors or mediators, such as obesity, smoking, hypertension and diabetes, are implicated in interactions between COVID-19 and CVD[7], and prevention and management of these risk factors and diseases should be maintained. However, the increased risk of CVD described by Xie et al was regardless of age, race, sex, CVD risk factors or pre-existing CVD. Therefore, even individuals at low risk of CVD can be at risk of CVD post-COVID. In addition, non-hospitalised individuals are at risk of CVD even though CVD risk increases by severity of acute COVID-19[7].

There are currently no evidence-based therapies for prevention or management of Long COVID. Vaccinations and anti-viral medications are effective in reducing the impact of acute COVID-19 and there is some evidence of reduction of risk of Long COVID. Future randomised trials and observational studies need to now consider Long COVID and CVD as outcomes. In addition, future trials must investigate the effect of CVD risk factor modification strategies on prevention and/or treatment of Long COVID, which could offset the increased risk of incident CVD and multi-organ morbidity in the long term.

Long COVID can affect multiple organs over time, but disease subtypes are yet to be fully characterised by symptoms or investigations. Although there is evidence of high burden of normal investigations in individuals with Long COVID[9], Xie et al demonstrate that investigation strategies of cardiac and multi-organ function in Long COVID need evaluation for effectiveness and cost effectiveness, whether imaging and blood biomarkers.

Care

The best way to avoid Long COVID, including COVID-19's CVD sequelae, is primary prevention. Infection control strategies to avoid SARS-CoV-2 infection are still important, especially in groups at increased risk of CVD, who should continue to be prioritised for vaccination and booster doses.

CVD and Long COVID require coordinated approaches to prevention, treatment and rehabilitation. The former requires lifelong healthcare consideration, and long-term prognosis and recovery of the latter is yet to be defined, although the 1-year risk of CVD shown by Xie and colleagues confirm that long-term follow-up should occur in certain individuals. The concept of "integrated care" has become central to several long-term conditions, including chronic obstructive pulmonary disease and heart failure, and should be implemented and evaluated in Long COVID. Research studies are underway to investigate care at the same time as examining mechanisms and trajectories of Long COVID, such as the LOCOMOTION (LOng COvid Multidisciplinary consortium Optimising Treatments and servIces across the NHS) and STIMULATE-ICP (Symptoms, Trajectory, Inequalities and Management: Understanding Long-COVID to Address and Transform Existing Integrated Care Pathways)[10]. Diagnosing and treating underlying conditions (including CVD) and risk factors is important for Long COVID care. Comorbidity and multi-morbidity are risk factors in CVD and Long COVID, but not fully analysed by Xie et al. Multimorbidity and frailty are associated with incidence and progression of CVD, and should prompt CVD risk screening and optimisation[11], to ensure evidenced-based prevention and management. Few studies focus on interventions for CVD risk among multimorbid patients, despite differences in CVD prognosis by multimorbidity clusters. Such studies are needed in Long COVID as well. Multidisciplinary, integrated care pathways, including CVD and multimorbidity, are necessary in Long COVID.

Personalised risk prediction is recommended in CVD[12] and in acute COVID-19[13]. Informatics and data science approaches are required in population-scale electronic health records such the study by Xie and colleagues to develop practical risk prediction tools for Long COVID.

Conclusions

There are bidirectional relationships between CVD and COVID-19 directly, indirectly and in the longer term. Multimorbidity and CVD are key considerations in Long COVID, which requires multidisciplinary, integrated care. Long COVID, including CVD complications, has potentially far-reaching resource implications for health systems, including staffing, infrastructure, and finances. The gaps in science, evidence and care need to be addressed together to enable effective and timely care for people with Long COVID. Future pandemic planning and preparedness should include modelling and consideration of CVD and non-communicable diseases and potential long-term sequelae.

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Figure 1. The learning health system approach to gaps in science, evidence and care for cardiovascular disease, multimorbidity and Long COVID.